solvents" and "when introduced" into these media (i.e. the processed or finalized carrier is subsequently introduced into same) the carrier has special properties (e.g. increased saturation solubility).

Applicants respectfully submit that the abstract of Muller does not describe at all in which dispersion medium the carrier is prepared. The dispersion medium used in Muller to prepare the carrier thereof is **water**, as clearly described throughout the specification thereof.

In contrast, in the present invention, an anhydrous or water-reduced medium is used. The present invention solves the problems associated with using water in a piston-gap homogenizer. It has been found that water vapor creates bubbles in a piston-gap homogenizer, which subsequently implodes (= cavitation) to lead to particle diminution. This problem is avoided by the present invention. Since Muller does not disclose using an anhydrous or water-reduced medium in the piston-gap homogenizer, Muller cannot anticipate the claim invention.

Arguments in Response to col. 20, lines 35-40 of Muller

Column 20, lines 35-40 of Muller is claim 38. Claim 38 of Muller describes a method in which as part of the process "subjecting at least one solid therapeutically active compound dispersed in a **solvent** to high pressure homogenization....". When one introduces a compound into a **solvent**, - as the word solvent says – the compound would **dissolve**, and not be in the form of small particles any more. Thus the process of claim 38 of Muller as it is worded will not yield in nanosized particulate carrier particles, because the active ingredient would **dissolve**. The method of claim 38 of Muller yields a **solution**.

In contrast to this, according to the present invention the active ingredient is **dispersed** in a **non-solvent**, i.e. medium, which results in a **suspension**. This suspension is then subjected to high pressure homogenization to yield a nanosuspension. Thus, Muller does not contain any teaching how to produce nanosized solid carriers in a non-solvent medium. For this reason alone, Muller cannot anticipate the claimed invention.

In view of the differences between Muller and the claimed invention, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1-20 and 22-45 under 35 U.S.C. § 103 as being unpatentable over WO 98/14174 (Desai) is respectfully traversed. The claimed invention is not obvious over Desai for the reasons of record and for the following reasons.

The Examiner states that one of ordinary skill in the art would be motivated to make paclitaxel or itraconazole compositions according to methods disclosed in the cited prior art wherein the methods have been shown to provide advantages of reduced volumes and low toxicity products.

It might be assumable that one would have tried to make such small drug nanoparticles, but the essential question is: Would the disclosure of Desai lead one of ordinary skill in the art to the present invention?

The Examiner admits that in Desai, "the drug is **dissolved** in an organic solvent." See page 3 of the Office Action. In contrast, in the claimed method the matrix material is not dissolved in the anhydrous or water-reduced medium. It remains in solid particle form as a **dispersion**.

Desai teaches the preparation of a **nanoemulsion**, plus subsequent additional steps to obtain drug particles in the nano-meter range. Disruption of large **droplets of a liquid** requires "relatively" low forces (compared to disrupting solids) and appears feasible.

In contrast to this, solids are much more rigid due to their crystalline and solid character. From the Desai disclosure one would **not be motivated** to process **solid drugs** using the same process.

As discussed previously, Applicants have now found that during homgenization using a piston-gap homogenizer, water vapor can be created in the form of bubbles, which subsequently implode. The resulting implosion shock waves lead to particle diminution. However, many materials are destroyed, melted or otherwise undesirably altered by these violent shock waves. See page 3, last paragraph to page 4, first paragraph, in the present translated application.

Applicants have solved these problem by providing a far more gentler method of obtaining the same particle size without using the implosion shock waves:

1) reducing the temperature of the medium being homogenized; and/or

2) reducing or eleminating the use of water.

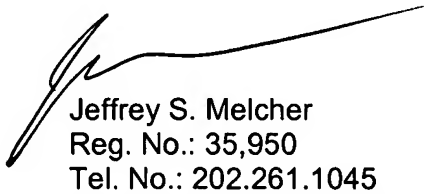
As discussed above, prior to the present invention, it was believed throughout the art that cavitation is the main source of diminution, as a consequence high pressure homogenization is generally described in water and especially increased effectiveness is claimed when homogenizing at higher temperatures. The reason for the increased efficiency at higher temperatures is the increased vapour pressure of water at higher temperature which provides increased cavitation. Therefore, the general teaching is the need to use water at higher temperatures to provide increased cavitation formation from water vapor to thereby provide particle diminution.

Contrary to this teaching, according to the present invention homogenization is performed in media other than water (anhydrous) or water reduced, and/or at lower temperatures to reduce or avoid cavitation from water vapor. Surprisingly, a comparable size diminution can be obtained without using destructive implosion shock waves. Contrary, to the general knowledge in the art, Applicants have found that cavitation is not the dominating diminution principle in the present invention. This is further supported by performing homogenization at lower temperatures, e.g. at 0° Celcius or below. A surprisingly similar efficiency in diminution is observed, which is contrary to the general beliefs in the art.

Desai does not disclose homogenizing solid particles and Desai does not address the problems associated with implosion shock waves from water evaporation. For these reasons, the Section 103 rejection should be withdrawn.

In view of all of the rejections of record having been addressed, Applicants submit that the claimed invention is in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,
Manelli Denison & Selter, PLLC

By 

Jeffrey S. Melcher
Reg. No.: 35,950
Tel. No.: 202.261.1045
Fax. No.: 202.887.0336

Customer No. 20736